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REVIEW ARTICLE

Evidence-Based Recommendations for Cancer Nausea and Vomiting

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ABSTRACT

The experience of patients living with cancer and being treated with chemotherapy often includes the symptoms of nausea and vomiting. To provide a framework for high-quality management of these symptoms, we developed a set of key targeted evidence-based standards through an iterative process of targeted systematic review, development, and refinement of topic areas and standards and consensus ratings by a multidisciplinary expert panel as part of the RAND Cancer Quality–Assessing Symptoms Side Effects and Indicators of Supportive Treatment Project. For nausea and vomiting, key clinical standards included screening at the initial outpatient and inpatient visit, prophylaxis for acute and delayed emesis in patients receiving moderate to highly emetic chemotherapy, and follow-up after treatment for nausea and vomiting symptoms. In addition, patients with cancer and small bowel obstruction were examined as a special subset of patients who present with nausea and vomiting. The standards presented here for preventing and managing nausea and vomiting in cancer care should be incorporated into care pathways and should become the expectation rather than the exception.

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INTRODUCTION

Nausea and vomiting are common symptoms in cancer patients as a result of either treatment-related toxicity or complications directly or indirectly related to the cancer. Regardless of the etiology, the symptoms of nausea and vomiting can interfere with patients' nutritional status and their enjoyment of eating and drinking and can significantly impact their quality of life. We are increasingly learning how to effectively prevent and manage such episodes; therefore, nausea and vomiting need to be appropriately prevented, screened, assessed, treated, and followed up to ensure the best possible care.

In cancer patients receiving chemotherapy, the incidence, prevalence, and severity of nausea and vomiting are related to several factors, most notably the emetic risk of the chemotherapy (related to the specific drug, dose, schedule, and route of administration) and patient variability. Overall, approximately 70% to 80% of cancer patients on chemotherapy experience nausea and/or vomiting.[1] Moreover, a negative experience with these symptoms leads to the subsequent impact of 10% to 44% of patient experiencing anticipatory nausea and/or vomiting.[2,3]

There are many types of neuroreceptors that are involved in the emetic response, including serotonin (5-hydroxytryptamine-3 [5-HT_3]), dopamine, corticosteroid, and neurokinin-1 receptors; therefore, antiemetic agents often target different neuroreceptors and can behave synergistically when used in combination.[4] Without the use of prophylactic antiemetic therapy, some highly emetic types of chemotherapy, such as cisplatin, would almost universally result in nausea and/or vomiting, but with the use of optimal antiemetic therapy, clinicians can reduce the prevalence to approximately 25% of patients on highly emetic therapy.[5,6] Therefore, appropriate pharmacologic prevention and management are essential.

Nausea and vomiting also occur in cancer patients not receiving chemotherapy or radiation, often as a result of disease involving the GI tract or abdomen. Malignant bowel obstruction is also common, particularly in advanced colorectal and ovarian cancer, and was addressed in detail as part of this project. Other common causes include constipation; dysmotility, which may be related to use of opioids or medications with anticholinergic properties; brain metastases; metabolic abnormalities, such as hypercalcemia; medication adverse effects; and gastric outlet obstruction. A review found rates of nausea and vomiting ranging from 4% to 44%, depending on cancer site and stage of disease.[7]

We undertook a research project to define quality standards for supportive cancer care. To do so, we attempted to define what research evidence,

clinical expertise, and consensus about the prevention and management of nausea and vomiting would support a minimum set of practices that would be required as part of good care. This article presents a clinical review and summary of clinical practice recommendations that supports the need for minimum standards in oncology practices to routinely address symptoms of nausea and vomiting in patients as a result of either chemotherapy or other causes, such as bowel obstruction.

METHODS

This report is part of the RAND Cancer Quality–Assessing Symptoms Side Effects and Indicators of Supportive Treatment Project, which was conducted from October 2007 to October 2008. This project developed an evidence-based, clinically useful set of tools that can be feasibly measured using medical charts to evaluate critical aspects of supportive cancer care practice. First, we conducted targeted systematic reviews to augment previously published reviews.[8,9] Then, a five-clinician team including experts in oncology, palliative medicine, and ethics prioritized symptoms related to cancer, treatment-related toxicities, and information and care planning needs for quality indicator development. Nausea and vomiting was identified as a priority on the basis of its prevalence, likely impact on patient and family quality of life, existing indicators, and the strength of medical evidence. For the consensus rating process, we requested nominations for nine expert panelists from major professional societies representing medical oncology, nursing, and social work and from our advisory group. The panelists represented geographically diverse academic and community settings. Panelists reviewed supporting evidence and rated validity and feasibility (for obtaining information from medical records) for each proposed indicators on a 9-point scale. Next, panelists met for review of the ratings and further discussion and then rated the indicators a second time. Of the 19 quality indicators for nausea and vomiting submitted to the expert panel, 16 were rated as valid and feasible, supporting the notion that they represent minimum standards of care.

This report describes the evidence related to such quality indicators for nausea and vomiting. Articles were identified through MEDLINE, the Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects, and the Cochrane Register of Clinical Trials (1997 to 2007). We limited searches to English language, using terms combined with each topic area (detailed search strategies are provided in Appendix Table A1, online only). To enrich the literature review, we searched for earlier citations selectively. In addition to relevant material from previous systematic reviews, we evaluated guidelines and quality indicators published after 2004 using the National Guideline Clearinghouse, National Quality Measures Clearinghouse, and Web sites of professional societies, medical organizations, and patient advocacy groups. Google searches made use of key words related to potential indicator topics. In the following sections, we summarize the findings by subcategories of care for nausea and vomiting.

SCREENING

A large, multicenter prevalence study found the highest rates of nausea and vomiting among palliative care patients with advanced cancers that affect the GI tract or abdomen, including gynecologic (42%), gastric (36%), esophageal (26%), and colorectal cancer (22%). Rates were also notable among other palliative care cancer patients (eg, 14% in lung cancer).[7] In addition, a recent systematic review of 44 studies, with a total of 25,074 patients with incurable cancer, demonstrated the prevalence of nausea and vomiting to be 31% and 20%, respectively.[10]

Evidence regarding rates of nausea and vomiting specifically with chemotherapy is covered in the following section. Nausea and vomiting are a standard part of the palliative care assessment as recommended by cancer palliative care clinical practice guidelines.[11] In summary, given the prevalence of nausea and vomiting, experts agree that it is prudent to routinely assess these symptoms at every outpatient visit and within 24 hours after an inpatient admission (Table 1).

PROPHYLAXIS

Developing and defining precise emetic risk categories is a challenging effort given the diversity of chemotherapy options and combinations and the individual patient characteristics that mitigate the risk. Efforts were made to develop emetic classifications that accounted for drug dose and route/rate of administration,[12] and the combination of systematic reviews and expert panels translated these efforts into a working classification that was incorporated into consensus and clinical practice guidelines in 1998 (revised in 2006) for both the American Society of Clinical Oncology (ASCO)[13] and the Multinational Association of Supportive Care in Cancer (MASCC).[8,9,14] The emetic risk categories are as follows: high ($>$ 90% emetic risk), moderate ($>$ 30% to 90% emetic risk), low (10% to 30% emetic risk), and minimal ($<$ 10% emetic risk). The recent consensus and clinical practice guidelines make antiemetic recommendations based on these risk categories. However, there is little in the way of stratification of emetic risk in terms of patient age, coexisting illnesses, polypharmacy, or the use of tobacco or ethanol.

An important consideration is the lack of practical tools to implement routine screening for emetic risk. Determining and documenting the emetic risk, given the diversity of combination chemotherapy and the heterogeneity of the cancer patient population, may be too time consuming for an individual clinician to carry out in practice. Nevertheless, there are important steps that clinicians can take to prevent nausea and vomiting.

In summary, providers should evaluate the emetic potential of every regimen and target high- and medium-risk situations for prevention, although documentation of emetic risk for every regimen may be impractical (Table 1).

HIGH EMETIC POTENTIAL

Until 2003, the standard antiemetic therapy for chemotherapy with high emetic risk was a combination of a 5-HT_3 receptor antagonist and dexamethasone. For our study, we examined four randomized studies (one phase II study and three phase III studies) that have addressed the addition of aprepitant to the standard regimen. These studies compared a three-drug regimen of a 5-HT_3 receptor antagonist, dexamethasone, and selective neurokinin-1 receptor blocker (aprepitant) with a two-drug regimen consisting of just a 5-HT_3 receptor antagonist and dexamethasone alone in the setting of cisplatin-based chemotherapy. These studies all showed a significant reduction in acute (day 1) emesis (7% to 17% in three-drug arm *v* 19% to 33% in two-drug arm; $P < .001$).[5,6,15,16] Pooled results from two of these randomized phase III trials demonstrated that patients without acute emesis (day 1) were 15% less likely to

Table 1. Recommendations for Managing Nausea and Vomiting in Cancer Patients

Recommendation	Evidence		
	Literature*	Guidelines†	Panel‡
Screening			
Assess for nausea and vomiting at every outpatient visit and within 24 hours of an inpatient visit on all cancer patients	III	Yes	Yes
Prophylaxis			
Evaluate the emetic potential of every chemotherapy regimen and target high and medium emetic risk situations for prevention	III	Yes	No
Prophylaxis: high emetic risk			
Use aprepitant in a three-drug regimen to prevent acute emesis and in a two-drug regimen to prevent delayed emesis	I	Yes	Yes
Prophylaxis: breast cancer patients on anthracyclines			
Use aprepitant in a three-drug regimen to prevent acute emesis and in a two-drug regimen to prevent delayed emesis	I	Yes	Yes
Prophylaxis: moderate emetic risk			
Use a two-drug regimen (5-hydroxytryptamine-3 receptor antagonist and dexamethasone) to prevent acute emesis and either one of these two drugs to prevent delayed emesis	I	Yes	Yes
Prophylaxis: low emetic risk			
Use dexamethasone, if clinically appropriate, to prevent acute emesis	I	Yes	No
Prophylaxis: nonpharmacologic			
Consider electroacupuncture if technique is available and performed by a capable operator	I	No	No
Postchemotherapy follow-up			
Provide some form of mutually understood communication plan to the patient for reporting acute symptoms	III	No	Yes
Treatment of nausea and vomiting			
Present alternative treatment options to a patient with persistent symptoms within 1 month in outpatient setting and within 48 hours within an inpatient setting	III	Yes	Yes
Bowel obstruction			
Treat with one of these approaches (surgery, stenting, decompression percutaneous gastrostomy tube, nasogastric tube, or octreotide) during an admission, and then assess within 48 hours if the approach is effective or not	I-III	Yes	Yes

*Level I: randomized clinical trials; level II: nonrandomized controlled trials, cohort or case analysis, or multiple time series; level III: textbooks, opinions, and descriptive studies.
†Guidelines sources include National Comprehensive Cancer Network, American Society of Clinical Oncology, Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer, and Cancer Care Ontario.
‡Panelists reviewed supporting evidence and rated validity and feasibility (for obtaining information from medical records) for each recommendation.

have delayed emesis ($P < .01$). Moreover, there was an improvement in quality of life using a functional living index, with 74% of patients in the aprepitant arm reporting minimal or no impact on daily life as a result of nausea or vomiting compared with 64% of patients in the control arm ($P < .01$).[17,18] Moreover, the data suggested that aprepitant negates the adverse prognostic factor of sex (women having a higher likelihood of emesis) in patients receiving highly emetic chemotherapy.[19] As a result, a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone, and selective neurokinin-1 receptor blocker administered before highly emetic chemotherapy has been incorporated into both the MASCC and ASCO guidelines (Table 2).[8,9]

In addition, these randomized studies addressed the role of aprepitant in prophylaxis of delayed (day 2 to 4 or 5) emesis. Two phase III, multicenter, randomized, placebo-controlled trials were performed comparing the two-drug regimen of the selective neurokinin-1 receptor blocker aprepitant plus dexamethasone on subsequent postchemotherapy days versus dexamethasone alone. These individual studies and a pooled analysis demonstrated that the two-drug arm with aprepitant had significant reduction in delayed emesis compared with the dexamethasone arm (24% to 32% in two-drug arm *v* 45% to 53% in dexamethasone arm; $P < .001$).[5,6,17,18] Moreover, there was an improvement in quality of life using a functional living index, with 74% of patient in the aprepitant arm reporting minimal or no impact on daily life as a result of nausea or vomiting compared with 64% of patients on the control arm ($P < .01$). The third randomized phase III controlled study compared postchemotherapy aprepitant plus dexamethasone with 5-HT_3 plus dexamethasone and demonstrated that the aprepitant arm was still superior for delayed protection against emesis (21% with emesis *v* 36%, respectively; $P < .001$).[16] As a result, a two-drug regimen including dexamethasone and a selective neurokinin-1 receptor blocker administered on days 2 and 3 after highly emetic chemotherapy has been incorporated into both the MASCC and ASCO guidelines (Table 2).[8,9]

In summary, extensive evidence and experts support the use of a three-drug regimen for the prevention of acute emesis in highly emetic regimens as a minimum standard of care and the use of a two-drug regimen for the prevention of delayed emesis in such regimens (Table 1).

MODERATE EMETIC RISK IN BREAST CANCER TREATMENT WITH ANTHRACYCLINES

Until recently, the standard antiemetic therapy for chemotherapy with moderate emetic risk was a combination of a 5-HT_3 receptor antagonist and dexamethasone. In a randomized, controlled, double-blind, phase III study of 866 patients undergoing anthracycline and cyclophosphamide treatment for breast cancer, patients in the experimental arm were treated with a three-drug regimen (with aprepitant) on day 1 and with aprepitant alone on

Table 2. Summary of Prophylaxis Trials

Emetic Potential	% of Patients With Emesis	*P*	Study
High emetic potential: > 90% risk			
Acute: day 1			
5-HT_3 antagonist, dexamethasone, aprepitant	7-17	< .001	Hesketh et al[5]; Poli-Bigelli et al[6]; Navari et al[15]; Schmoll et al[16]
5-HT_3 antagonist, dexamethasone	19-33		
Delayed: days 2-4			
Dexamethasone, aprepitant	24-32	< .001	Hesketh et al[5]; Poli-Bigelli et al[6]; Warr et al[17]; de Wit et al[18]
Dexamethasone	45-53		
Dexamethasone, aprepitant	21	< .001	Schmoll et al[16]
5-HT_3 antagonist, dexamethasone	36		
Moderate emetic potential: breast cancer with anthracycline			
Acute and delayed: days 1-5			
5-HT_3 antagonist, dexamethasone, and aprepitant on day 1 followed by aprepitant alone on days 2 and 3	24	< .001	Herrstedt et al[20]
5-HT_3 antagonist and dexamethasone followed by 5-HT_3 antagonist alone on days 2 and 3	43		
Moderate emetic potential: 30%-90% risk			
Acute: day 1			
5-HT_3 antagonist	34	< .001	Cubeddu et al[21]
Placebo	88		
5-HT_3 antagonist plus dexamethasone	25	< .001	Jantunen et al[22]
5-HT_3 antagonist	60		
Delayed: days 2-4			
Dexamethasone	13	< .02	The Italian Group for Antiemetic Research[23]
Placebo	23		
5-HT_3 antagonist plus dexamethasone	8	NS	The Italian Group for Antiemetic Research[23]
Dexamethasone	13		

Abbreviations: 5-HT_3, 5-hydroxytryptamine-3; NS, not significant.

days 2 and 3. The control arm was treated with a two-drug regimen (without aprepitant) on day 1 and with only a 5-HT_3 receptor antagonist on days 2 and 3. The use of aprepitant in the experimental arm decreased day 1 to 5 emesis compared with the control arm (24% with emesis *v* 41%, respectively; $P < .001$).[24] This benefit also translated into a quality-of-life benefit using a functional living index, which demonstrated that 63.5% of patients on aprepitant had no or minimal impact on daily life compared with 55.6% of patients on the 5-HT_3 arm ($P < .019$). This study was extended to compare the treatment arms over four cycles of treatment. The treatment advantage of aprepitant was not only maintained but slightly increased in cycles 2, 3, and 4 of chemotherapy.[20] As a result, both the MASCC and ASCO guidelines recommend a three-drug regimen including single doses of a 5-HT_3 receptor antagonist, dexamethasone, and selective neurokinin-1 receptor blocker in breast cancer patients undergoing treatment with an anthracycline and cyclophosphamide (Table 2).[8,9]

In summary, evidence and experts support the use of aprepitant to prevent acute and delayed emesis in breast cancer patients on anthracycline and cyclophosphamide chemotherapy (Table 1).

MODERATE EMETIC RISK

Initially, the use of 5-HT_3 receptor antagonists and dexamethasone was used to treat highly emetogenic chemotherapy.[25] Subsequently, 5-HT_3 receptor antagonists have been studied with regard to moderately emetic chemotherapy. A randomized phase III clinical study in patients receiving cyclophosphamide showed that 5-HT_3 receptor antagonists are better than placebo in preventing emesis (34% *v* 88%, respectively; $P < .001$).[21] A subsequent meta-analysis examined 11 randomized trials (including the aforementioned trial) that used 5-HT_3 receptor antagonists with moderately emetic chemotherapy; the meta-analysis demonstrated that the risk of acute emesis was decreased with the use of 5-HT_3 receptor antagonists (odds ratio = 0.47; 95% CI, 0.39 to 0.58) and that the risk was further reduced when drugs in this class were combined with dexamethasone (Table 2).[22]

There are now six drugs in the class of 5-HT_3 receptor antagonists (dolasetron, granisetron, ondansetron, palonosetron, ramosetron, and tropisetron). Multiple randomized trials have been performed that have demonstrated that these agents are generally equivalent in both antiemetic activity and safety.[26] Meta-analyses and additional randomized phase III clinical trials that have compared agents in this drug class have demonstrated similar efficacy.[27,28] One of the most recent drugs in this class has been intravenous palonosetron, which has both a longer half-life and a higher binding affinity to the 5-HT_3 receptor. Although there is a suggestion that this new agent may be superior to others in its class, the randomized trials were designed to demonstrate noninferiority rather than superiority. Both the MASCC and ASCO guidelines do not recommend one 5-HT_3 agent over another.[8,9]

Previous recommendations by MASCC and ASCO[13,14] for prophylaxis against delayed emesis from chemotherapy of moderate

emetic risk included not only single-agent dexamethasone and a 5-HT_3 receptor antagonist, but also the combination of the two. The superiority of dexamethasone over placebo in preventing delayed emesis in patients receiving moderately emetogenic chemotherapy has been demonstrated in previous randomized phase III trials.[29] The data with respect to 5-HT_3 antagonists are mixed. A meta-analysis of eight randomized placebo-controlled trials evaluating the use of 5-HT_3 antagonists to prevent delayed emesis after moderately emetic chemotherapy showed only a minimal reduction in relative risk (RR) of emesis (RR = 0.92, $P = .016$),[30] and subsequent analysis casts doubt on the cost-effectiveness of using 5-HT_3 receptor antagonists for the prevention of delayed emesis.[31]

One of the larger studies included in the meta-analysis discussed earlier was a three-arm, phase III, randomized controlled trial (RCT) that compared placebo versus dexamethasone versus dexamethasone plus a 5-HT_3 antagonist. This trial demonstrated that dexamethasone was superior to placebo in decreasing delayed emesis (87% *v* 77%, respectively; $P < .02$), but that dexamethasone plus 5-HT_3 antagonist was not superior to dexamethasone alone (92% *v* 87%, respectively), and the combination was associated with more constipation.[23] A recent phase III RCT compared dexamethasone versus a 5-HT_3 antagonist and demonstrated equivalency with respect to both control of emesis and quality of life from nausea and vomiting symptoms (Table 2).[32] The MASCC recommendations indicate that, for the prevention of emesis in this category, dexamethasone is the preferred agent, with 5-HT_3 antagonists as an alternative, whereas the ASCO guidelines recommend both equally.[8,9]

In summary, extensive evidence and experts support the use of a two-drug regimen for the prevention of acute emesis in moderately emetic regimens and the use of either dexamethasone or a 5-HT_3 antagonist for the prevention of delayed emesis in such regimens (Table 1).

LOW EMETIC RISK

There are no RCTs looking at the appropriate antiemetic therapy with chemotherapy of low emetic risk. The recommendation to use dexamethasone is based on the substantial evidence of the benefits of this agent with regard to controlling chemotherapy-induced nausea and vomiting in moderate to highly emetic chemotherapy. A meta-analysis of 32 RCTs involving 5,613 patients demonstrated that dexamethasone was superior to placebo or no treatment for complete protection from acute emesis (odds ratio = 2.22; 95% CI, 1.89 to 2.60)[33] and for complete protection from delayed emesis (odds ratio = 2.04; 95% CI, 1.63 to 2.56).[34] As a result of the effectiveness of dexamethasone, expert panels have reached moderate consensus regarding this agent with chemotherapy regimens of low emetic risk, and this recommendation has been included in both the MASCC and ASCO guidelines.[8,9]

In summary, although there may be evidence to support the use of dexamethasone for the prevention of acute emesis in low emetic regimens, experts believe that clinicians should make the decision based on the specific chemotherapy being used and the characteristics of the patient (Table 1).

NONPHARMACOLOGIC PROPHYLAXIS

There are a variety of acupuncture-point stimulation techniques that have been examined in treating chemotherapy-induced nausea, vomiting, or both. These techniques include methods that involve needles, electrical stimulation, magnets, or acupressure. Compared with pharmacologic therapy, the number of randomized trials and the number of patients for which these nonpharmacologic therapies have evaluated are limited. A recent systematic review and meta-analysis examined 11 RCTs pooling 1,247 patients.[35] The use of acupuncture-point stimulation of all methods (needles = acupuncture; electrical stimulation plus needles = electroacupuncture; electronic stimulation plus pressure but no needles = noninvasive electrostimulation; or pressure but no needles = acupressure) reduced the incidence of acute emesis (RR = 0.82; 95% CI, 0.69 to 0.99; $P = .04$) but not the symptom of acute or delayed nausea compared with controls. By modality, stimulation with needles reduced the proportion of acute vomiting (RR = 0.74; 95% CI, 0.58 to 0.94; $P = .01$) but not acute nausea severity. Moreover, it seems that the major effect was a result of electroacupuncture (RR = 0.76; 95% CI, 0.60 to 0.97; $P = .02$) rather than manual acupuncture. Acupressure reduced the acute nausea severity but not acute vomiting. Noninvasive electrostimulation was not beneficial.[36,37]

One of the larger RCTs examined the combination of electroacupuncture and traditional antiemetic therapy in 104 high-risk breast cancer patients receiving high-dose chemotherapy. This trial demonstrated that the addition of electroacupuncture significantly ($P < .001$) decreased the number of emesis episodes (five episodes) over a 5-day period compared with either minimal needling (10 episodes) or pharmacology alone (15 episodes).[38] The use of nonpharmacologic modalities has not been adopted and incorporated yet into the MASCC or ASCO guidelines. Some considerations that weigh on whether clinicians should be expected to use acupuncture include the facts that the competency in the use of these nonpharmacologic techniques is variable and difficult to assess by referring physicians and that electroacupuncture is not readily available in all geographic areas.

In summary, evidence supports electroacupuncture by clinicians competent in its administration for chemotherapy-induced nausea (Table 1).

FOLLOW-UP

As indicated in the previous section, there is a substantial likelihood of acute nausea and vomiting even with optimal antiemetic therapy. For example, with highly emetic chemotherapy regimens, approximately 11% to 17% of patients still have acute emesis even with a three-drug regimen, and approximately 25% to 32% of patients still have delayed emesis even with an optimal two-drug regimen.[5,6] Defining the minimum standard for appropriate follow-up of patients at risk for nausea and vomiting is challenging. Some advocates may feel that the responsibility for follow-up falls on the shoulders of the health provider, whereas others may feel that the patient should be responsible for reporting an adverse symptom or complication from therapy.

In summary, experts feel that providing some form of mutually understood communication plan between the health care professional

and patient for reporting acute symptoms is an integral part of providing patient care (Table 1).

MULTIPLE OPTIONS TO TREAT NAUSEA AND VOMITING

There are many pharmacologic options that may improve nausea and vomiting in cancer patients. A systematic review of antiemetics for nausea in advanced cancer[39] included RCTs comparing metoclopramide with placebo that found that metoclopramide was superior and an RCT comparing ondansetron with metoclopramide that found no difference. Response rates in these RCTs were low (23% to 36% for nausea and 18% to 52% for vomiting). Other antiemetics had only weak evidence from uncontrolled studies or case series, or there was no evidence. A systematic review of the use of haloperidol for nausea and vomiting in palliative care[40] found only uncontrolled case series and case reports. We found one additional RCT, which studied the addition of dexamethasone to metoclopramide for nausea in advanced cancer in 51 patients,[41] that found no significant benefits for any symptoms. A systematic review of the adverse effects of opioids, including in cancer-related pain, found six RCTs. Three of these trials addressed currently available antiemetics for opioid-induced nausea and vomiting, including droperidol, ondansetron, and cyclizine, which all demonstrated significant efficacy compared with placebo.[42] MASCC, ASCO, and the National Comprehensive Cancer Network guidelines recommend multiple options to treat nausea and vomiting in the cancer patient.[8,9,11]

In summary, evidence and experts support a multitude of alternatives for managing nausea and vomiting. As such, alternative treatment options should be presented to a patient with persistent symptoms within 1 month in outpatient setting and within 48 hours within an inpatient setting (Table 1).

BOWEL OBSTRUCTION: A SPECIAL CASE

Malignant bowel obstruction is common in advanced cancer, especially in ovarian and colorectal cancers. Moreover, individuals with malignant bowel obstruction often have pain, nausea, and vomiting. Emergency surgical intervention is not generally necessary but is often appropriate in patients with a reversible cause, good performance status, and lack of complicating factors; stents are an appropriate alternative in many situations. Given the role of complicating factors in causing symptoms, obstruction may reverse spontaneously or with medical treatment, and a trial may be warranted before more invasive treatment is initiated. A variety of symptomatic approaches have also been used for patients with obstruction judged to be inoperable or who would be at high surgical risk.[43] Patients with symptomatic malignant bowel obstruction should be offered at least one of the following treatments during admission: surgery, stenting, decompression percutaneous gastrostomy tube, nasogastric tube, or octreotide.

A systematic review through 2005 of studies comparing stenting with surgery for malignant large bowel obstruction identified 10 studies, including two RCTs, but none evaluated quality of life or long-term symptom management as an outcome.[44] We identified no additional RCTs. A systematic review of stenting[45] found 32 case series with a total of 606 patients; placement was successful in 97% of patients, and resolution of symptoms was described in 89% of these patients. There were severe complications in 1%, stent migration in 5%, and obstruction in 18%.

A 1999 Cochrane review identified 24 retrospective and one prospective case series of surgery.[46] There was marked variability in the denominators and in how symptom control was defined and measured; reports of symptom control, found in 12 studies, ranged from 42% to 80%, and rates of recurrent obstruction, reported in 13 studies, ranged from 10% to 15%. With respect to surgery, we found no clinical trials, but the 2001 European Association for Palliative Care clinical practice guideline recommended that surgery not be conducted in patients with poor prognostic indicators, such as massive ascites, poor performance status, or poor nutritional status; 30-day mortality in the 24 case series cited by the guideline ranged from 9% to 41%.[43]

For placement of a decompression percutaneous endoscopic gastrostomy tube, although we identified no clinical trials, numerous case series cited in the European Association for Palliative Care review[43] describe high rates of symptom resolution; for example, one study[47] described successful placement in 21 of 22 referred patients with complete resolution of nausea and vomiting; in another study,[48] successful placement was possible in 32 of 34 referred patients, 84% of patients had symptomatic relief, and there were no major complications.

One clinical practice guideline on octreotide, based on a systematic literature review updated through 2004, recommended the use of octreotide in patients with inoperable bowel obstruction.[49] The review identified two RCTs, and we identified one additional RCT in our search; all three studies compared octreotide with hyoscine. The largest RCT[50] enrolled 68 terminally ill cancer patients judged inappropriate for surgery (maximum survival was 61 days). Both groups received chlorpromazine and either morphine or fentanyl. There was a significantly greater decrease in nausea and vomiting, fatigue, and anorexia in the octreotide group compared with the hyoscine group ($P < .05$), although there was no significant difference in pain. An additional RCT enrolled 18 patients, 15 of whom had data available for analysis.[51] There were significant reductions in vomiting at 24 and 48 hours ($P < .01$) and nausea at 48 and 72 hours ($P < .03$) between the two groups. The third RCT, including 17 patients with inoperable obstruction and a nasogastric tube,[43] found that, for the 10 hospitalized patients, nausea was significantly lower ($P = .05$) in the scopolamine group, but there was no difference for pain. For both of these two RCTs, although patients were not randomly assigned to hydration, patients receiving less hydration had significantly more nausea (although hydration was strongly associated with other factors, such as whether the patient was hospitalized). We did not find any RCTs addressing the efficacy of anticholinergics (such as hyoscine) or hydration. The evidence, based on two systematic reviews and two RCTs did not support recommending corticosteroids as a treatment option.[39,52-54]

In summary, given the diversity of options supported by evidence and experts (surgery, stenting, decompression percutaneous gastrostomy tube, nasogastric tube, or octreotide), patients should be treated with one of these approaches during admission and then assessed within 48 hours to determine whether the approach is effective (Table 1).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

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